RESEARCH ARTICLE

Albumin-globulin Ratio for Prediction of Long-term Mortality in Lung Adenocarcinoma Patients

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Abstract

Background: Prior studies showed a relationship between serum albumin and the albumin to globulin ratio with different types of cancer. We aimed to evaluate the predictive value of the albumin-globulin ratio (AGR) for survival of patients with lung adenocarcinoma. Materials and Methods: This retrospective study included 240 lung adenocarcinoma patients. Biochemical parameters before chemotherapy were collected and survival status was obtained from the hospital registry. The AGR was calculated using the equation AGR=albumin/(total protein-albumin) and ranked from lowest to highest, the total number of patients being divided into three equal tertiles according to the AGR values. Furthermore, AGR was divided into two groups (low and high tertiles) for ROC curve analysis. Cox model analysis was used to evaluate the prognostic value of AGR and AGR tertiles. Results: The mean survival time for each tertile was: for the 1st 9.8 months (95%CI:7.765-11.848), 2nd 15.4 months (95%CI:12.685-18.186), and 3rd 19.9 months (95%CI:16.495-23.455) (p<0.001). Kaplan-Meier curves showed significantly higher survival rates with the third and high tertiles of AGR in comparison with the first and low tertiles, respectively. At multivariate analysis low levels of albumin and AGR, low tertile of AGR and high performance status remained an independent predictors of mortality. Conclusions: Low AGR was a significant predictor of long-term mortality in patients with lung adenocarcinoma. Serum albumin measurement and calculation of AGR are easily accessible and cheap to use for predicting mortality in patients with lung adenocarcinoma.

Keywords: Albumin-globulin ratio - lung adenocarcinoma - survival

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Introduction

Non-small cell lung cancer (NSCLC), which includes a broad range of lung tumors encompassing squamous cell carcinomas and adenocarcinomas as the major subtypes, is the most common cause of cancer related death (Jemal et al., 2010). In patients with lung adenocarcinoma, only a few parameters are described as a prognostic factors such as stage of disease, tumor metabolism, high GLUT1 expression and performance status (de Geus-Qei et al., 2007; Andersen et al., 2011).

Serum total proteins contain albumin, globulins and other inflammatory proteins such as C-reactive protein (CRP), interleukins and tumor necrosis factors (McPherson et al., 2006). Albumin and globulins play a pivotal role in the inflammatory process (Azab et al., 2013). Serum albumin is also an objective parameter that reflects the degree of long-term nutrition status (Laky et al., 2007). The globulins play an important role in immunity and chronic inflammation and reflects a cumulative exposure of different cytokines (Azab et al., 2013). Albumin to globulin ratio (AGR=albumin/(total protein-albumin) is the ratio of serum albumin to non-albumin proteins. Investigators have demonstrated that hypoalbuminemia is an independent predictor of long-term mortality in several cancers including gastric, colorectal and breast (Onate-Ocana et al., 2007; Gupta et al., 2010; Azab et al., 2013). In this study, for the first time, we aimed to evaluate the predictive value of the serum AGR for long-term mortality in lung adenocarcinoma.

Materials and Methods

This retrospective study included consecutively 330 patients with histologically confirmed lung adenocarcinoma at Medical Oncology Clinic of Erciyes University Hospital in Turkey between January 2007 and January 2011. The records of 330 patients were reviewed based on the following inclusion criteria: (1) patient was pathologically diagnosed with lung adenocarcinoma, (2) normal renal and liver functions; (3) patient had complete pre-treatment serum total protein and albumin level

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Table 1. Baseline Characteristics of the Patients by AGR Tertiles.

Variables	1st AGR tertile n=80	2nd AGR tertile n=80	3th AGR tertile n=80	p1	p2
Age (years)	60 ± 10	59 ± 10	57 ± 10	0.825	0.080
BMI (kg/m2)	24.2 ± 4.6	25.6 ± 5.1	26.6 ± 4.5	0.116	0.005
Gender (male, n.%)	69 (86.2)	67 (83.7)	58 (72.5)	0.692	0.046
Smoking (n.%)	57 (71.3)	54 (67.5)	48 (60.0)	0.732	0.183
Diabetes (n.%)	12 (15.0)	4 (5.0)	10 (12.5)	0.062	0.819
Hypertension (n.%)	13 (16.3)	16 (20.0)	18 (22.5)	0.682	0.424
Cardiac disease (n.%)	10 (12.5)	10 (12.5)	5 (6.3)	1.000	0.278
COPD (n.%)	3 (3.8)	6 (7.5)	7 (8.8)	0.495	0.328
Total protein (gr/dl)	7.0 ± 0.6	6.9 ± 0.6	6.8 ± 0.6	0.381	0.075
Albumin (gr/dl)	3.0 ± 0.4	3.5 ± 0.3	3.9 ± 0.3	<0.001	<0.001
Globulin (gr/dl)	3.9 ± 0.4	3.4 ± 0.3	2.9 ± 0.3	<0.001	<0.001
AGR (%)	0.7 ± 0.1	1.0 ± 0.1	1.4 ± 0.2	<0.001	<0.001
AST (U/L)	23 (7-107)	23 (9-87)	22 (8-77)	0.911	0.685
ALT (U/L)	22 (6-103)	29 (6-109)	25 (4-99)	0.021	0.258
WBC (k/cc)	9.9 ± 4.2	9.5 ± 4.4	9.0 ± 3.8	0.572	0.184
Hemoglobin (mg/dl)	12.8 ± 1.6	13.3 ± 2.0	13.4 ± 2.0	0.148	0.061

*COPD: Chronic obstructive pulmonary disease, AGR: albumin-globulin ratio, BMI: body mass index, WBC: white blood cell. p1: difference between 1st tertile *vs* 2nd tertile, p2= difference between 1st tertile *vs* 3th tertile.

records; (4) patient had complete follow-up data.(5) Stage 3 or 4 patients at the diagnosis. Exclusion criterias were as follows: (1) patient underwent surgery; (2) patients who had preexisting liver disease; (3) patients with chronic inflammatory disease including autoimmune disorder and infection. A total of 240 patients matched the inclusion and exclusion criteria. Patients information, disease stage and laboratory datas prior to therapy were retrieved from the patient records. The AGR was calculated using the equation AGR=albumin/(total protein-albumin). AGR values of patients are ranked from lowest to highest and the total number of patients were devided into three equal tertiles according to the AGR values (1th tertile was contain 80 patients with the lowest AGR values and 3rd tertile was contain 80 patients with the highest AGR values). Furthermore, patients were devided two groups by value of AGR 1.01 according to the ROC analysis (see statistic section). Group 1 consisted of 107 patients and Group 2 consisted of 133 patients. Albumin values of patients also ranked from lowest to highest and the total number of patients were divedid in to three equal tertiles according to the albumin levels like AGR tertiles. Survival analysis was used to evaluate the prognostic value of AGR, AGR tertiles, albumin and low-high groups of AGR. The primary endpoint was all-cause mortality. The patients were followed through January 2014 for the primary endpoint, which was obtained from the hospital cancer registry. The study was approved by the institutional review board.

The tumor size (T), lymph node status (N), presence of metastasis (M) and the American Joint Committee on Cancer (AJCC) stage for each patient were obtained from patients data in our cancer registry (Grene et al., 2002).

Statistic

Statistical analysis was performed using the SPSS 19.0 software package. The continuous variables (according to the normality of the distribution) were presented as means±standard deviations or median with minimum-maximum levels. Categorical variables were presented as percentages. AGR tertiles were analyzed using either the chi-square test for categorical variables or the One-way Anova test for continuous variables. Receiver operating characteristics (ROC) analysis was performed. The best cutoff value was determined and the sensitivity and specificity at that point were determined (Figure 1). Survival rates were analyzed using the Kaplan-Meier method and were compared using the logrank test. A Univariate analyse was performed for each variable that may potential predictors of mortality using the Cox proportion-hazards model. Those variables, which found tobe statistically significant (p<0.05) were included in a multivariate Cox regression model. Statistical significance was defined as p<0.05.

Results

Comparision of AGR tertiles according to the baseline characteristics

Level of ALT was significantly lower in 1st AGR tertile than in 2nd AGR tertile (p=0.021). BMI was significantly lower in 1st AGR tertile than in 3rd AGR tertile (p=0.005). Serum albumin level and AGR were significantly lower, serum globulin level was significantly higher in 1st AGR tertile than 2nd and 3rd tertiles (p<0.001 for all, Table 1).

Primary outcome

The mean survival time for each tertile was: for the 1th tertile; 9.8 months (95%CI:7.765-11.848), for the 2nd tertile; 15.4 months (95%CI:12.685-18.186), and for the 3rd tertile; 19.9 months (95%CI:16.495-23.455) (p<0,001). Kaplan-Meier curves showed significantly higher survavial rates in the second and third tertile of AGR and albumin comparison with the first tertile of AGR and albumin (Figure 2).

Table 2 presents the association between baseline characteristics and overall survival in patients with lung adenocarcinoma (univariate Cox analysis). In our study, high levels of aspartate transaminase and white blood cell were associated with higher risk of mortality (p=0.002 and p=0.019 respectively). In addition, low levels of albumin and AGR were associated with higher risk of mortality (p=0.001 and p=0.021 respectively). Also low level of hemoglobin was associated with higher risk of mortality

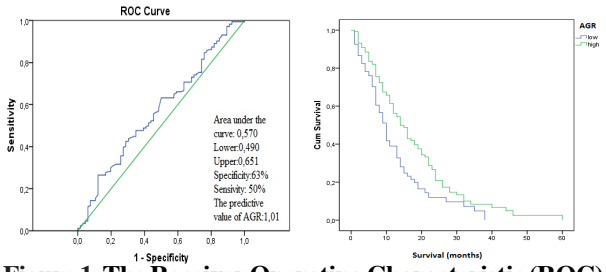

Figure 1. The Receiver Operating Characteristic (ROC) Curve for Albumin-globulin Ratio for Predicting Lung Adenocarcinoma Mortality and Kaplan-Meier Survival Curves Stratified by AGR Groups which was Determined by ROC Curve Analysis (p=0.001)

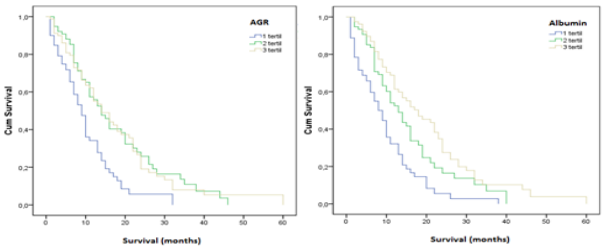

Figure 2. Kaplan-Meier Survival Curves Stratified by Albumin-globulin Ratio (AGR) Tertiles and Albumin Tertiles (p<0.001 for both)

but not statistically significant (p=0.051). Lower mortality was noted in patients with 3rd tertile of AGR compare with 1st tertile of AGR. The mortality rate of 2nd and 3rd tertile of AGR was not significantly different. The hazard ratio of the patients in the 1st AGR tertile increased by 1.680 (p=0.026) in comparison with those in the 3rd AGR tertile (Table 2).

According to the ROC curve analysis

The predictive value of AGR for mortality from lung adenocarcinoma (sensitivity of 63% and specificity of 50%, area under the ROC curve=0.570) was 1.01 (Figure. 2). We devided all patients by value of AGR 1.01. Group 1 consisted of 107 patients and Group 2 consisted of 133 patients. The mean survival time for low AGR group was 12.1 (95% CI:8.551-11.449) and for high AGR group was 17.4 months (95% CI:11.307-166939) (p=0.001). Kaplan-Meier curves showed significantly higher survavial rates in the Group 2 (higer AGR group) than in the Group 1 (lower AGR group) (Figure 1).

Multivariate analysis

Table 3 presents the multivariate analysis by Cox proportional hazard models. We included the variables that associated with survival status in univariate Cox analyses. High levels of white blood cell and low levels of albumin and AGR remained an independent predictors of mortality (Table3). Furthermore low tertile of AGR (become 1st AGR tertile) and bad performance status were an independent predictors of mortality (Table 3).

Discussion

The main finding of our study was that low levels of pretreatment albumin and AGR are an independent and

Table 2. Hazard Ratios of Baseline Characteristics for All-cause Mortality in Patients with Lung Adenocarcinoma (Univariate Analysis)

Variable	Hazard ratio (95% CI)	P value
Age	1.008 (0.990-1.027)	0.367
Body mass index	0.967 (0.924-1.012)	0.152
Gender	0.863 (0.479-1.554)	0.623
Smoking	1.518 (0.890-2.589)	0.125
Diabetes	1.200 (0.655-2.199)	0.486
Hypertension	1.076 (0.627-1.847)	0.791
Cardiac disease	1.330 (0.656-2.695)	0.429
Total protein	1.024 (0.728-1.440)	0.891
Albumin	0.436 (0.266-0.717)	0.001
Aspartate transaminase	1.025 (1.009-1.042)	0.002
Alanine transaminase	0.989 (0.975-1.003)	0.134
Hemoglobin	0.883 (0.779-1.001)	0.051
White blood cell	1.047 (1.008-1.087)	0.019
Performance (ref: zero)		
Performance 1	1.902 (1.289-2.807)	0.001
Performance 2	2.378 (1.239-4.563)	0.009
AGR	0.418 (0.199-0.876)	0.021
AGR (ref: 3rd tertile)		
AGR 1th tertile	1.680 (1.063-2.654)	0.026
AGR 2nd tertile	0.865 (0.562-1.330)	0.509

*AGR: Albumin-globulin ratio

Table 3. Cox Proportional Multivariate Hazard Models for All-cause Mortality in Patients with Lung Adenocarcinoma

Variables	Hazard ratio (95%CI)	P value
AGR	0.288 (0.151-0.552)	<0.001
Performance 1 *vs* 0	1.600 (1.145-2.235)	0.006
Performance 2 *vs* 0	2.509 (1.516-4.151)	<0.001
Albumin	0.398 (0.285-0.557)	<0.001
AGR 1th tertile *vs* 3rd tertile	1.968 (1.341-2.888)	0.001
AGR 2nd tertile *vs* 3rd tertile	1.028 (0.709-1.489)	0.885
White blood cell	1.048 (1.012-1.085)	0.009

*AGR: Albumin-globulin ratio

significant predictor of long-term mortality in patients with lung adenocarcinoma. Previous studies showed that a low AGR was predictive for poor survival in breast cancer (Azab et al., 2013), colorectal cancer (Azab et al., 2013) and nasopharyngeal carcinoma (Du et al., 2014), To the best of our knowledge, this is the first study to specifically focus on the predictive value of the AGR in lung adenocarcinoma.

Serum albumin is produced by the liver and maintains osmotic pressure, buffers blood pH and plays a role in the transport of hormones, fatty acids and other compounds. Serum albumin has antioxidant function, acts as a free radical scavenger, play a role in hemostasis of calcium and steroid hormones, and has inhibitor effect on cancer cell lines (Laursen et al., 1990; Sonnenschein et al., 1996). Serum albumin is used to assess patient nutritional status, disease progression, severity and prognosis in hospital (Laursen et al., 1990; Sonnenschein et al., 1996).

Hypoalbuminemia is frequent in hospitalized patients and malnutrition, chronic inflammation, nephrotic syndrome and liver disease suppress albumin synthesis (Yeun et al., 1998). Some studies showed that chronic

inflammation may play a more important role than malnutrition (Gabay et al., 1999; Cueto et al., 2001; Kaysen et al., 2002). Hypoalbuminemia has a strong predictive value on mortality and morbidity regardless of its cause (Gatta et al., 2012). Up to now, hypoalbuminemia has been reported as an independent negative prognostic factor for survival in several cancers including lung (Gupta et al., 2010), gastric (Onate-Ocana et al., 2007), colorectal (Azab et al., 2013) and breast (Gupta et al., 2010). Also low serum albumin level was shown to be an important prognostic factor for tumor recurrence and correlate with poor survival in NSCLC patients (Jin et al., 2013; Yildirim et al., 2013).

Similar to these results, in our study, we observed that patients with decreased albumins had poor survival compared to those with high albumin in patients with lung adenocarcinoma. In our study, while patients with BMI < 18 kg/m^2 were considered as malnutrition, only 8 patients in our group had BMI <18 kg/m^2. Thus, we propose that the prognostic value of low albumin and AGR could solely be explained by chronic inflammation, and malnutrition does not play an important role in our study patients.

Chronic inflammation markers (a part of the calculated globulins) play an important role in the proliferation, progression, development and metastasis of tumor cells (Mantovani et al., 2008; Gatta et al., 2012; Guo et al., 2013; Unal et al., 2013). They also significantly associated with angiogenesis, risk of reccurence and survival in patients with cancer. (Gabay et al., 1999; Mantovani et al., 2008; Yildirim et al., 2013). In several studies, high inflammatory parameters (CRP, alpha and gamma globulins, neutrophil lymphocyte ratio (NLR), complement C3-C4) were found and associated with reduced overall survival in patients with different cancers including lung cancers (Shimada et al., 2003; Canna et al., 2005; Kaya et al., 2013; Zheng et al., 2013; Dai et al., 2014; Soliman et al., 2014). Increasing synthesis of acute phase proteins and interleukins and tumor necrosis-related hypoxia may be the mechanisms underlying this increased inflammation (McMillan et al., 2009). In our study, level of white blood cell was an independent predictor of mortality in patients with lung adenocarcinoma (Table 3). So, we showed that the association between chronic inflamation and mortality, similar to the studies so far.

Previous studies reported that pretreatment AG) is an independent and significant predictor of long-term mortality in breast, colorectal and nasopharyngeal cancer patients (Azab et al., 2013, Du et al., 2014). Using this ratio is very plausible because it contain both important parameters that predicting long term mortality in cancer patients: albumin and globulin (which contain chronic inflammation parameters). We propose that AGR can be used as prognostic marker in patients with lung adenocarcinoma. Additionally, we suggest that AGR is superior to serum albumin in predicting mortality in cancer population for a couple of reasons. First, the low AGR is a combination of two important predictors of adverse outcome, low albumin and high globulin. So, AGR might predict mortality better than the other two parameters (albumin and nonalbumin proteins). Second, some conditions such as dehydration and fluid retention may affect the serum consantration of albumin and globulin but AGR would be unaffected by these conditions. In our study, low levels of AGR was a predictor of poor outcome in patients with lung adenocarcinoma patients.

The major limitations of this study were the retrospective single-center design and lack of measurement of specific inflammatory markers such as CRP and cytokine levels.

In conclusion, pretreatment low AGR is an independent predictor of poor survival in patients with lung adenocarcinoma. Calculation of AGR is easily accessible and cheap to use laboratory method for predicting mortality in patients with lung adenocarcinoma. AGR may be more useful than albumin because of AGR would be unaffected by some conditions that affect albumin and nonalbumin proteins and AGR is a superior prognostic factor in its incorporation of both variables. Further studies are needed to include AGR and other prognostic factors in risk stratification models.

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